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Randomized evaluation of live attenuated vs. inactivated influenza vaccines in schools (RELATIVES) pilot study: A cluster randomized trial

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ABSTRACT

Background: School-based influenza immunization can effectively address accessibility barriers, but injected inactivated influenza vaccines (IIV) may not be acceptable to some children and parents in school settings.
Objectives: To better understand the feasibility of offering intranasal live attenuated influenza vaccines (LAIV) through schools, we assessed uptake, stakeholder acceptability, and cost of school-based delivery of LAIV compared to IIV.
Methods: We piloted an open-label cluster randomized trial involving 10 elementary schools in Peterborough, Ontario during the 2013–2014 influenza vaccination campaign. Schools were randomized to having students receive IIV or LAIV at publicly-funded school-based clinics organized by the local public health department. We measured the percentage of students vaccinated with at least one dose of influenza vaccine at school. Stakeholder acceptability was evaluated through a questionnaire of parents and interviews of public health department personnel and school principals. We compared the costs per dose of vaccine administered, including staff time and costs of vaccines and supplies.
Results: Single-dose influenza vaccine uptake was higher for the five schools offering LAIV than for the five offering IIV (19.3% vs. 12.2%, $p = 0.02$). Interviews with nine school principals and five public health department personnel suggested that the clinics ran smoothly with little disruption to school routines, and that LAIV was associated with increased efficiency and calmer children. All interviewees cited unfamiliarity with LAIV and the study recruitment package length as potential reasons for low uptake. The cost per vaccine dose administered was $38.67 for IIV and $43.50 for LAIV.
Conclusions: Use of LAIV in school-based clinics was associated with increased vaccine uptake and the perception among immunizing staff of reduced child anxiety, but also slightly higher vaccine administration

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costs, compared to IIV. However, uptake was low for both groups. More effective strategies to promote influenza vaccines and to obtain parent consent may improve vaccine uptake.
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1. Introduction

Seasonal influenza causes increased mortality, health services utilization, and work and school absenteeism every year [1–5]. Ontario, Canada's most populous province, introduced universal publicly funded influenza immunization in 2000, offering free influenza vaccines for all individuals aged 6 months or older [6]. These are accessible through institutions (e.g. hospitals, long-term care facilities), physician offices, public health-organized clinics, workplace clinics, and pharmacies. Vaccinating children may be an effective strategy for influenza control because of their high influenza attack rates [7–9]. However, despite the availability of free immunization, during the 2006–2007 influenza season, influenza vaccine coverage was only 31% among children aged 12–19 years, 28% among healthy children aged 2–11 years, and 37% among children aged 2–11 years with chronic health conditions [10], far lower than the >70% coverage observed among adults aged 65 years or older [11]. One reason for not being immunized is having barriers to access, such as lack of transportation and personal and family responsibilities [12–14].

Analogous to established Ontario-wide public health programs providing vaccinations against hepatitis B virus, human papillomavirus, and meningococcal disease through schools [15], school-based influenza immunization has been considered as a strategy to overcome access barriers. Since 2000, it has been implemented at the discretion of each of Ontario's 36 public health departments, and has been associated with increased coverage and decreased physician visits among school age children [11]. Ontario parents appreciate the potential convenience of immunizing children against influenza at school but retain several concerns including children being afraid of needles and requiring parental comfort during vaccination [16].

Live attenuated influenza vaccine (LAIV) is an alternative to injected inactivated influenza vaccines (IIV). LAIV was approved for use in the United States in 2003 and in Canada in 2010. Canada's National Advisory Committee on Immunization recommends it over IIV for healthy children between 2 and 17 years, based on immunogenicity, efficacy, and effectiveness data in young children [17]. A meta-analysis of three clinical trials involving 13,000 healthy children aged 6 months to 17 years demonstrated that compared to IIV, receipt of LAIV reduced the risk of laboratory-confirmed influenza by 45–53% in vaccine-naïve children (6 to 71 months) and 35% in previously vaccinated older children (6–17 years) [18]. Providing LAIV through schools has been associated with increased coverage and decreased influenza-like illness in school age children [9,19]. However, at this time in Ontario, only IIV is publicly funded. The use of LAIV as part of the province's universal influenza immunization program is currently under review.

We conducted a pilot study to evaluate the feasibility of administering LAIV vs. IIV via schools by determining the effect of influenza vaccine type on uptake, stakeholder acceptability, and cost. Since the intervention is at the level of the school, with the hypothesis that providing LAIV to children at school will lead to increased vaccine uptake, we used a cluster design.

2. Methods

During the 2013–2014 influenza vaccination campaign, we conducted an open-label cluster randomized trial involving elementary schools (Junior Kindergarten [age 4] to Grade 8 [age 13]) within the geographic boundaries of the Peterborough County-City Public Health Unit (PCCHU). This local public health department is responsible for a mixed urban-rural community (population ~145,000) 125 km northeast of Toronto, Ontario. In September and October 2013, 10 of 28 schools belonging to the Kawartha Pine Ridge District School Board agreed to participate. Participating schools and non-participating schools were similar in rural representation (40% vs. 44% of all schools, respectively, with rural location defined as having a zero in the second position of their 6-digit postal code, indicating an area that is not accessible by letter carriers) [20]. Using a standard computer pseudorandom number generator, the schools were randomized by JAP on a 1:1 basis to having all students offered IIV or LAIV at publicly-funded school-based influenza immunization clinics organized by PCCHU.

In October 2013, 10-page recruitment packages comprising an introductory letter, a study consent form, a vaccine consent form, and a Frequently Asked Questions document were sent home with all students. Parents/guardians (hereafter referred to as "parents") were requested to return the study consent form, and if they wished to have their child/dependent (hereafter referred to as "children") vaccinated at school, the vaccine consent form as well. Each school used at least two promotional tools to inform parents of the study (e.g., automated voice messages, email distribution lists, school websites, school signs).

Between November 11 and 22, 2013, public health nurses conducted an immunization clinic at each school for students for whom parental consent had been obtained. At intervention schools, students without contraindications to LAIV were immunized with a 0.2 ml dose of intranasal LAIV (FluMist®) [17]. IIV was available for children whose parents declined LAIV but still wanted their child immunized against influenza. At control schools, students who did not have a contraindication to IIV were immunized with a 0.5 ml dose of intramuscular IIV (Vaxigrip®) [17]. The nurses returned to each school within two weeks to vaccinate children who had been absent during the first clinic, or whose parents had forgotten to submit their vaccine consent form. Children aged younger than 9 years who had not previously received influenza vaccine required two doses, however, the second dose was not administered at school. Parents were instructed to have their child receive the second dose at least four weeks after the first dose via their primary care physician or a community-based public health clinic.

All parents who provided an email or mailing address on the study consent form were contacted in February 2014 and invited to complete an Internet- or paper-based questionnaire on behalf of their children. The questionnaire asked about demographics, risk factors for influenza, receipt of influenza vaccines during the current influenza season, and adverse events following immunization. Two reminders were sent out to parents who had not yet completed a questionnaire (in two- or four-week intervals for emailed and mailed questionnaires, respectively). Respondents received a $5 Starbucks gift card as an incentive to complete the questionnaire.

2.1. Uptake

We used the number of children who had received one dose (by vaccine type) of influenza vaccine given at school-based clinics as the numerator, and the student census as of January 1, 2014 (provided by each school) as the denominator, to calculate school-level vaccine uptake.

2.2. Safety

As per public health guidelines, public health nurses monitored children for 15 min following vaccination. Parents/guardians were asked to contact the study team if their child experienced any symptoms during the following five days. Public health nurses followed up with parents who reported an event. The study questionnaire also asked parents to indicate whether their child had experienced any adverse event in the 7 days following receipt of influenza vaccine at school.

2.3. Stakeholder acceptability

The stakeholders of interest were all parents with children attending these 10 schools, school principals of these schools, and PCCHU personnel who participated in the school-based clinics or assisted in organizing them. We assessed parental perceptions of school-based immunization with LAIV and IIV through the questionnaire, which included questions about perceived safety, effectiveness, and acceptability of influenza vaccines.

The school principals and PCCHU's immunization program manager and immunizing nurses were invited to participate in one-on-one telephone interviews with JAP. Interviews with school principals focused on their experiences with coordinating the program, facilitators/barriers to its continued existence, and relevant interactions with parents and teachers. Interviews with public health personnel focused on perceptions of the program and of administration of IIV vs. LAIV, based on experiences with clinic coordination and vaccine delivery.

2.4. Cost

We performed a cost comparison of school-based administration of IIV versus LAIV. The following costs were obtained from PCCHU: associated equipment (syringes, needles, alcohol wipes, cotton balls, plastic bandages, tissues), staff time spent on campaign coordination, communication with parents/guardians at clinics, vaccine delivery, and post-vaccination monitoring. Vaccines are bulk purchased by Ontario's Ministry of Health and Long-Term Care, so the cost per dose of vaccine was obtained from the Ministry.

2.5. Analysis

Continuous variables were compared using two sample *t* tests and proportions were compared using chi-square tests or Fisher's exact tests. To compare school-level vaccine uptake between the two arms, we performed a weighted *t* test to adjust for clustering and to take variation in student population size into account [21]. Two-sided tests were used for all statistical analyses. We used STATA version 10.0 (2007, StataCorp, LP, College Station, TX) for analyses.

The interviews were reviewed to facilitate an exploration of emergent themes [22]. At least two team members read each transcript once to get an overall sense of the data, and then again to identify major topics or issues.

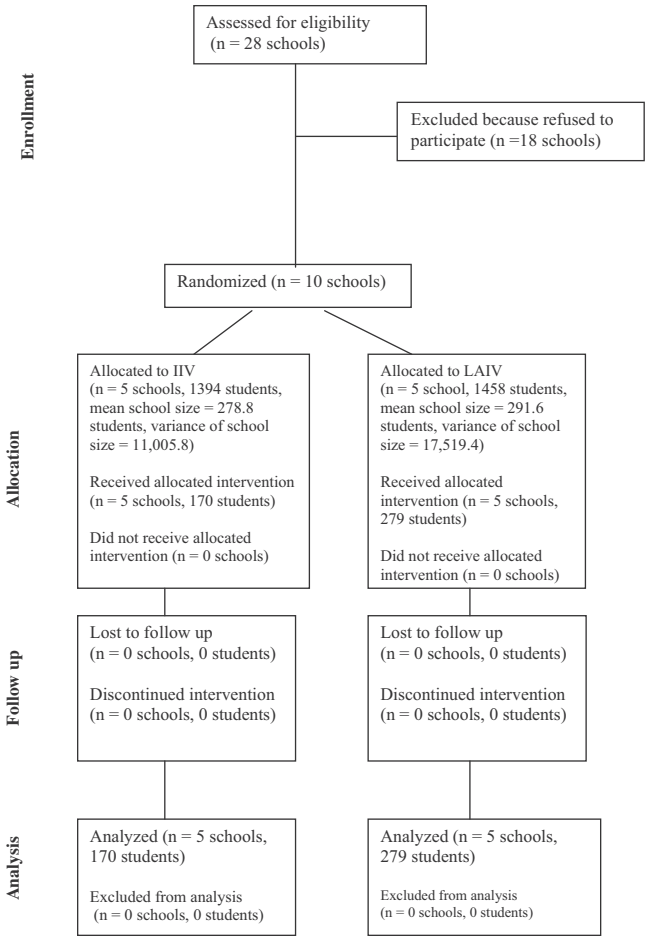

Fig. 1. Enrollment and follow-up of study participants.

2.6. Sample size

To calculate the sample size required to detect a 10% increase in uptake with LAIV compared to IIV, we used the sample size calculation for two proportions based on 80% power and alpha = 0.05 (two-sided). The unit of randomization was the school. To account for the clustering effect of schools, we inflated the sample size by 20% (i.e., variance inflation factor), resulting in a sample size of 451 students/group.

2.7. Ethics

This study was approved by Public Health Ontario's Ethics Review Board (Protocol 2013-24.04) and Kawartha Pine Ridge District School Board's Research Advisory Committee.

3. Results

Of the 28 eligible schools, 10 study schools (total number of students = 2852, range = 110–450 students per school) agreed to participate and were randomized; 5 were assigned to receive LAIV and 5 were assigned to receive IIV (Fig. 1).

Based on questionnaire responses from parents (response rates: 9.2% overall [262/2852], 7.7% [107/1394] for IIV schools, 10.6% [155/1458] for LAIV schools), the demographics of the two groups were similar (Table 1).

Table 1
Characteristics of the study population obtained from a questionnaire of parents[a].

	Responses from IIV[b] schools: $n = 107$ (%)[d]	Responses from LAIV[c] schools: $n = 155$ (%)[d]
Children's characteristics		
Female	54 (50.4)	79 (51.0)
Mean age (years) (standard deviation, range)	8.1 (3.5, 4–13)	8.2 (3.4, 4–14)
Body mass index (BMI)[e]		
Normal weight	67 (71.3)	101 (70.1)
Overweight	13 (13.8)	16 (11.1)
Obese	14 (14.9)	27 (18.8)
Has a regular doctor	103 (97.2)	155 (100)
Inhaled steroid use more than twice weekly	2 (2.0)	4 (2.7)
Long term aspirin user	0 (0)	1 (0.7)
Has a chronic disease[f]	7 (7.0)	15 (10.1)
Aboriginal status	3 (3.0)	6 (4.1)
Household members' characteristics		
Highest level of education attained by household members		
Less than high school	1 (1.0)	3 (1.9)
High school graduation	11 (10.6)	10 (6.5)
Post-secondary graduation	92 (88.5)	142 (91.6)
Household member with a weakened immune system	10 (10.0)	9 (6.2)
Household has one or more children aged 2 years or younger	10 (10.0)	26 (17.8)
Household member smokes	16 (15.8)	23 (15.9)
Children's vaccination history		
Vaccinated against influenza this season (Oct 2013 to Feb 2014)	89 (83.2)	136 (87.7)
Vaccinated against influenza last season (Oct 2012 to Feb 2013)	49 (51.6)	68 (50.0)
Vaccinated against influenza before October 2012	64 (68.1)	101 (76.5)
Had a severe reaction to a previous influenza vaccine	0 (0)	2 (1.4)
Had a negative reaction to any vaccine	7 (6.9)	6 (4.0)

[a] The study population consists of all children whose parents completed a questionnaire, including those who did not receive influenza vaccination at school.
[b] Inactivated influenza vaccine.
[c] Live attenuated influenza vaccine.
[d] Denominator of each response varies depending on completeness of data. Missing data and "don't know" responses were excluded from the analysis.
[e] BMI categories for children are based on the 2000 US Centers for Disease Control and Prevention Growth Reference.
[f] Chronic diseases included: asthma, diabetes, cancer, anaemia, heart disease, lung disease, kidney disease, blood diseases.

3.1. Uptake

LAIV-assigned schools had significantly higher single-dose uptake (279/1458; 19.3%, 95%CI 14.1–24.5%) than IIV-assigned schools (170/1394; 12.2%, 95%CI 7.8–16.5%) (difference = 7.2%, 95%CI 1.5–12.8%; $p = 0.02$) (Table 2).

3.2. Safety

No significant difference in the proportion of side effects experienced for children receiving IIV vs. LAIV (8.8% vs. 11.3%, $p = 0.62$) was observed.

3.3. Acceptability

3.3.1. Parents

Parents cited various reasons for having or not having their children vaccinated at school (Table 3). Some questionnaire respondents did not consent to school-based immunization for their children. Of the 37 children whose parents returned a questionnaire but did not receive vaccine at school clinics, 18 attended IIV schools and 19 attended LAIV schools. Fifteen of the 37 children were vaccinated in other settings: physician offices ($n = 6$), public health community-based clinics ($n = 5$), pharmacies ($n = 3$), and workplace clinics ($n = 1$).

Only 28.4% of all respondents were familiar with LAIV prior to the 2013–2014 influenza season. A significantly higher proportion of parents of children attending LAIV schools thought LAIV was more effective at preventing influenza than IIV (26.9% vs. 0%, $p < 0.001$) and was safer than IIV (26.9% vs. 9.6%, $p = 0.003$) (Table 4). If both vaccines were offered for free next year, parents at LAIV schools were more likely than parents at IIV schools to prefer their

Table 2
Single dose influenza vaccine uptake by type of vaccine offered at each school.

School	Number vaccinated	School population	Single dose vaccine uptake (%)
IIV[a] 1	20	110	18.2
IIV 2	42	300	14.0
IIV 3	14	230	6.1
IIV 4	51	424	12.0
IIV 5	43	330	13.0
IIV Total	**170**	**1394**	**12.2**
LAIV[b] 1	93	450	20.7
LAIV 2	35	280	12.5
LAIV 3	17	117	14.5
LAIV 4	35	180	19.4
LAIV 5	99	431	23.0
LAIV Total	**279**	**1458**	**19.3**

[a] Inactivated influenza vaccine.
[b] Live attenuated influenza vaccine.

Table 3
Parental vaccination behaviours and attitudes.

Behaviour or attitude (in reference to the 2013–2014 influenza season)	n (%)[a]
Vaccination status of respondent's child ($n = 261$)	
Received IIV[b]	92 (35.3)
Received LAIV[c]	132 (50.6)
Did not receive any influenza vaccine	37 (14.2)
Reasons child was not vaccinated against influenza ($n = 37$)	
Did not feel it was necessary	23 (62.1)
Concerned about negative side effects	14 (37.8)
I don't believe the vaccine is effective	12 (32.4)
Have not gotten around to it	3 (8.1)
Not convenient	1 (2.7)
The child is not eligible to receive the vaccine	1 (2.7)
Reasons child received influenza vaccine at school ($n = 157$)	
Convenience of school vaccination	124 (79.0)
School offered LAIV vaccine at no cost	92 (58.6)
Parent/guardian works full-time	27 (17.2)
Not sure where else to get child vaccinated	8 (5.1)
Child is better receiving vaccinations when parent is absent	7 (4.5)
Child preferred to be vaccinated with friends	4 (2.6)
Preferred non-injection vaccine over injection	3 (1.9)
No access to a car	1 (0.6)
Reasons child received influenza vaccine outside of school ($n = 11$)	
Parent wanted to be present while child was vaccinated	4 (36.4)
Parent wanted child to be vaccinated earlier than the school date	1 (9.1)
Parent did not want child to receive the vaccine offered at school	1 (9.1)
Parent would prefer child to be vaccinated by own healthcare provider	1 (9.1)
Child was absent on the vaccination day	1 (9.1)
None	2 (18.2)

[a] The percentages for some questions may add up to greater than 100% because respondents could select more than one response.
[b] Inactivated influenza vaccine.
[c] Live attenuated influenza vaccine.

Table 4
Comparison of parents' vaccine preferences based on school allocation.

Question	Responses from IIV schools, *n* (%)	Responses from LAIV schools, *n* (%)
Which vaccine do you think is more effective at preventing influenza in kids? (*n* = 202)		
LAIV	0	32 (26.9)
IIV	10 (12)	3 (2.5)
No difference	16 (19.3)	35 (29.4)
Neither are effective	1 (1.2)	0
Don't know	56 (67.5)	49 (41.2)
Which vaccine do you think is safer for kids? (*n* = 202)		
LAIV	8 (9.6)	32 (26.9)
IIV	8 (9.6)	5 (4.2)
No difference	23 (27.7)	45 (37.8)
Neither are effective	2 (2.4)	1 (0.8)
Don't know	42 (50.6)	36 (30.3)
[a]**Which vaccine do you feel more comfortable with your child receiving (*n* = 261)?**		
LAIV	17 (15.9)	90 (58.4)
IIV	19 (17.8)	7 (4.5)
No difference	50 (46.7)	36 (23.4)
Neither vaccine	15 (14.0)	19 (12.3)
Don't know	6 (5.6%)	2 (1.3)
[a]**Which vaccine would you prefer your child receive next year, assuming both vaccines are available for free (*n* = 260)?**		
LAIV	35 (32.7)	111 (72.5)
IIV	19 (17.8)	6 (3.9)
No preference	30 (28.0)	19 (12.4)
Neither vaccine	14 (13.1)	14 (9.2)
Don't know	9 (8.4)	3 (2.0)

[a] Parents could respond more than once if they had more than one child.

child receive LAIV (72.5% vs. 32.7%, $p < 0.001$), while the opposite pattern was observed for IIV (3.9% vs. 17.8%, $p < 0.001$).

Of the 259 parents who responded to our question about comfort with vaccine, 46 (17.8%) were uncomfortable with their child receiving LAIV; reasons included insufficient safety data (40.5%), belief that the vaccine is unnecessary (38.1%), and their child having no issues with IIV injection (33.3%). However, 53 (20.5%) of those 259 parents were uncomfortable with their child receiving IIV, with the main reason being the child's fear of needles (43.4%).

3.3.2. Principals

Nine of 10 school principals (one IIV principal declined to respond) were interviewed. The principals reported that school responsibilities during the clinics involved briefing teachers about the study, disseminating recruitment packages, reminding students to return forms, and implementing promotional activities. All principals stated that the clinics required minimal time commitment from school staff.

Seven principals indicated that their school's teachers expressed disappointment that staff could not be vaccinated at the school clinics. One principal from an IIV school reported that staff thought that the recruitment package was too large and complex for their students' parents (Fig. 2).

One principal from an IIV school recounted that a parent expressed concern that their child was being asked to try an untested vaccine. This principal felt that the word "study" may have implied that the vaccines' safety and efficacy were unproven.

All nine principals found the nursing staff to be very efficient with clinic processes. Principals at LAIV schools were particularly impressed, with three remarking on how the children seemed calmer than they do after receiving injectable vaccines at school (e.g., hepatitis B virus and human papillomavirus vaccines). To increase vaccine uptake, the principals recommended more promotion at the beginning of the school year, so that parents would be aware that the clinic was upcoming, and also be able to gain more familiarity with LAIV.

"My general feeling is that [LAIV clinics] went very well, very smoothly, better than injection, we had very few of the swooners that we usually get. I can almost predict which kids it's gonna be. I was really impressed with how it ran that day. I hope to see it become something of a regular practice." (Principal 3)

"I think with our population it's hard…they don't have time for consent forms, and we try to send out forms that are 1, maybe 2 pages max. Otherwise, they have no time for all of that." (Principal 1)

"I don't think school's the place for [SBII clinics]. It's just not a good place for vaccines. We're not equipped for it. The kids get so upset! Some don't even know what's going to happen, their parents didn't tell them so they're crying and upset, and it lasts all day. We're a school, we can't provide the comfort… we can't do the parenting. And I think a lot of our parents want us to do the parenting, they don't want to be there for that, they know their child will be upset so they'd rather we deal with it. But we're a school, we're not equipped to handle it." (Principal 6)

"I would say most of the kids were very accepting of the nasal mist. Much more so than of the injection… And [LAIV] was faster… You don't have as much getting ready with that" (Nurse 3)

Fig. 2. Quotes from stakeholders regarding school-based influenza immunization.

All principals understood that study materials had to contain more information than typical consent forms, but agreed that school forms should not exceed three pages. Three principals mentioned that their schools' families were of a low socioeconomic status, and were unlikely to read lengthy, text-heavy documents. One principal suggested that an abbreviated two-page package be developed to send home to every parent, advising them to pick up the full-sized package from the principal's office should they require additional information.

Principals generally thought that school-based influenza immunization is a good idea, and should continue, with the option for staff to be vaccinated. One principal wished to make his school a community hub, and thought the clinic should be open to the public. However, one principal at an IIV school thought that school-based clinics interfered with education, and that children with anxiety over needles often required comfort that teachers are unable to provide.

3.3.3. Public health department personnel

Individual telephone interviews were conducted with the immunization program nurse-manager and four of the five immunizing nurses (the fifth nurse was out-of-town and could not be contacted). The nurse responsible for scheduling the clinics stated that this process was very similar to the coordination that she does for other school-based immunization clinics, and it was facilitated by the mutual familiarity between her and school representatives.

All five of the nurses were satisfied with the clinics' organization, and they perceived that the LAIV clinics ran more quickly than IIV clinics due to less time required to reassure children and not needing to remove layers of clothing to administer vaccine. Two nurses perceived that children were calmer after LAIV administration compared to vaccination with IIV.

To improve uptake, the nurses suggested that vaccine promotion campaigns should begin earlier in the school year and to use media (radio and television) to provide information on the vaccines and clinic schedules. The nurses thought that the length of the recruitment packages likely served as a deterrent for participation. They heard from a few parents who were very satisfied with LAIV, since their children seemed to accept it much better than a needle. One interviewee mentioned that using electronic methods as an option for obtaining consent might be beneficial, since children may not bring back signed forms.

Table 5
Cost per vaccine dose administered.

Item	IIV[a]	LAIV[b]
Vaccine	$10.00	$20.00
Clerical staff time	$16.10	$16.10
Nursing staff time	$12.00	$7.30
Cotton ball	$0.005	N/A
Alcohol pads	$0.02	N/A
Needle/syringe	$0.42	N/A
Bandage	$0.13	N/A
Total	**$38.67**	**$43.40**

[a] Inactivated influenza vaccine.
[b] Live attenuated influenza vaccine.

3.4. Cost

The cost per dose of vaccine administered was $38.67 for IIV and $43.40 for LAIV (Table 5).

4. Discussion

This pilot study was conducted to better understand the feasibility of offering LAIV through schools, by comparing it to IIV delivery based on uptake, acceptability, and cost. LAIV uptake was higher than that for IIV, the main stakeholders of school-based clinics (parents, school principals, and immunization staff) were pleased with the process, and cost was comparable between the two arms. However, overall uptake was lower than expected, suggesting that further work is required to increase vaccine awareness in parents and to provide education regarding vaccine safety and efficacy.

We observed lower uptake than in recent school-based LAIV immunization studies in the UK and the US [9,23], possibly due to the length of the study recruitment package, the timing of the school clinics, and the availability of influenza vaccines through other settings. However, without confirmation from parents who opted out of the study, we cannot verify these explanations. PCCHU's typical vaccine consent forms are two pages or fewer but since this was a research study, and we assumed that parents had not previously heard of LAIV, it was necessary to provide them with additional information. We offered each school the option of a parent information session, but principals preferred other promotional activities. PCCHU could not schedule the clinics before mid-November due to competing priorities, but parents may have wanted their children vaccinated earlier in the season. In addition to physician offices and community-based public health clinics, influenza vaccines became available for the first time in pharmacies in Peterborough during the 2013–2014 influenza season, making vaccines more accessible for families who may have otherwise opted for school-based vaccination. We also heard from one nurse and one principal that offering a second school-based clinic in January would be beneficial, to capitalize on the established pattern of influenza vaccination rates plateauing until a second wave of vaccination requests is prompted by media reports of serious influenza complications (e.g., an influenza-related death).

The difference in uptake between IIV and LAIV schools may be partially explained by LAIV being offered for free in the study. Results from our questionnaire indicate that this was a key reason why parents of children at LAIV schools opted for vaccination through the school. Parents who wished to have their children vaccinated with LAIV would have had to pay for the vaccine outside of the study, whereas IIV is offered for free through universal publicly funded vaccination. The variations in vaccine uptake across all IIV and LAIV schools may be due to the varying promotional activities used at each school. Since they each had different pre-existing communication channels to alert parents to the study, we could not implement a consistent promotional plan across all schools.

Although IIV is a less costly vaccine than LAIV, when the costs related to vaccine administration are included, the overall cost per dose is comparable. More nursing hours are required with IIV, since time is spent removing layers of clothing to access the upper arm and convincing anxious children to receive a needle. The trade-off is that LAIV has more contraindications, so that nurses spend more time asking questions and confirming information.

Overall clerical and vaccine administration costs were likely higher for this study than for regular influenza vaccination clinics, due to the additional tasks involved (e.g., study record-keeping, follow-up with parents whose children had a minor adverse event following vaccination). Our results are aligned with a recent Canadian study that modelled the cost-effectiveness of LAIV and IIV for children aged 2–17 years and found LAIV to be associated with higher vaccination costs than IIV [24]. However, due to fewer anticipated influenza cases leading to reduced healthcare use and parents' work absenteeism, LAIV saved $4.20 and $35.34 per vaccinated child in direct and societal costs, respectively, compared to IIV.

Although LAIV has been used in the US since 2003, and has been approved in Canada since 2010, the questionnaire responses suggest that parents in Ontario are not familiar with it, which is to be expected since it is not publicly funded. Asking parents to consent to their children receiving an unfamiliar vaccine may have fostered the erroneous perception that we were studying a new and untested drug. The results of this study demonstrate that experience with LAIV is generally positive; parents who had their children vaccinated with LAIV were likely to believe it is safe and effective, and to feel comfortable with their child receiving it in the future. In a 2012 German study of 146 children vaccinated with LAIV, parents gave LAIV a mean acceptability rating of 1.55 (1 = very good, 6 = unacceptable), and 140 (97%) parents indicated they would opt for their child to receive LAIV again the following year [25].

Our interviews found that principals and nurses perceived that children were calmer after receiving LAIV than they typically are following receipt of an injectable vaccine. Although we did not obtain children's perceptions in this study, these observations corroborate a 2011 survey of US children aged 8–12 years that found nearly 70% preferred receiving influenza vaccine as an intranasal spray compared to an injection, and that mode of administration had the greatest impact on personal preference compared to other vaccine attributes [26].

This study had some limitations. This was an open-label trial, which could have introduced bias due to free availability of IIV but not LAIV outside of the study. We did not blind schools or students because we did not think using placebo injections and nasal sprays would be feasible. Vaccine uptake was lower than anticipated, which may have been partially due to the relatively late timing of the school-based immunization clinics. Although influenza vaccines were available to the public in early October, the local public health department was only able to conduct the school clinics in November because their nursing staff were already committed to school-based immunization clinics for other vaccines. The timing of school-based influenza immunization has been shown to be associated with uptake obtained [27]. Our questionnaire had a low response rate (9%), with most respondents being parents who had their child vaccinated. These parents could have been more informed about the benefits of vaccination or are more likely to seek preventive healthcare services compared to those who refuse vaccination, therefore the results from the questionnaire may be biased. Also, the information provided to parents focused on the vaccine to which their children's school was assigned (e.g., parents

at LAIV schools were informed that LAIV is more effective than IIV), which likely impacted their perceptions of the vaccines. Since we delivered information to parents by having students take paper recruitment packages home, we do not know if parents did not receive the package, they did not read it, they did not want to participate, or if students did not return the signed study consent forms (with the parent contact information for the questionnaire) to their teachers. Other studies have shown that parents perceive it important that multiple methods be used to deliver information and consent forms [28]. Furthermore, parents may have been confused by the inclusion of a study consent form requesting contact information for the questionnaire and a separate vaccine administration consent form. Separating delivery of the two consents may have increased the response from parents interested in providing opinions via a questionnaire but who did not want their children to be vaccinated at school. Finally, our survey respondents are not necessarily representative of the Ontario population as they were more likely to have their children vaccinated, but the results concerning acceptability from the school principals and public health department personnel should be transferable to other settings.

5. Conclusion

Our pilot study demonstrated that LAIV can be administrated in school clinics in an efficient manner with high stakeholder acceptability and comparable costs to IIV administration. Further work is required to increase uptake, including parental education, promotion of vaccine clinics at the start of the school year, and employing both online and paper-based methods to distribute information to parents.

The full trial protocol may be requested from the authors.

Conflict of interest statement

None declared.

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